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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,188	01/05/2000	BEN SHEN	2500.128US1	1369

22798 7590 03/11/2005

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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/478,188

Applicant(s)

SHEN ET AL.

Examiner

Kathleen M Kerr

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24,26-35,37,38,40 and 42-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24,26-35,37,38,40 and 42-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 September 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final action (Paper No. 20, mailed on March 19, 2002), Applicants filed an amendment to the claims and a response received on September 25, 2002. Said amendment canceled Claims 1-23, 25, 36, 39, 41, and 46-71 and amended Claims 24, 26, 27, 30, 32, 40, and 42-45. Thus, Claims 24, 26-35, 37, 38, 40, and 42-45 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/115,434 filed on January 6, 1999.

Also as previously stated and not rebutted by Applicants, the Examiner notes that ORF 28, an O-methyltransferase in the C-1027 gene cluster of *Streptomyces globisporus*, does not appear to be disclosed in the provisional application. Since methods using this ORF are the elected subject matter, none of the claims are granted priority to this date. Thus, the date used for prior art purposes herein is the filing date of the instant application, that is January 5, 2000.

Drawings

3. The drawings filed on September 25, 2002 have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Compliance with the Sequence Rules

4. Applicant's amendment to the description of Figure 7 and the sequence listing provided in both computer readable form (CRF) and paper copy filed on December 29, 2004 have been entered.

Applicant must provide a proper statement of sameness and no new matter for said sequence listing so that the instant application can be in full compliance with the sequence rules (as required by 37 C.F.R. § 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d)). The only statement filed on December 29, 2004 is that the CRF filed is identical to a previously filed paper copy; however, a paper copy was also filed on December 29, 2004. A proper statement signed by Applicant's representative is required.

Withdrawn - Objections to the Specification

5. Previous objection to the specification for the title is withdrawn by virtue of Applicant's amendment to the title.

6. Previous objection to the specification for being confusing is withdrawn with respect to sequences noted but maintained for other points below.

Maintained - Objections to the Specification

7. Previous objection to the specification for being confusing is on page 29, line 28, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that on page 29, line 28, beta amino acids are correctly recited. The Examiner maintains the objection to the specification because section (e) on this page is about

Art Unit: 1652

benzoxazolinates, not beta amino acids. It appears the language is copied from the previous section (d) wherein beta amino acids are described. Correction on page 29, line 29 from “beta amino acids” to ---benzoxazolinates--- is required or Applicant must clarify how making benzoxazolinates related to making beta amino acids.

8. Previous objection to the specification for the terms “epoxide hydase” and “epoxide hydrolase” being used somewhat interchangeably throughout the specification is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant argues that the terms are not used in the claims so the confusion cited by the Examiner is acceptable. That is not the case. As required by 35 U.S.C. § 112, second paragraph, the specification must be clear. If these enzymes are intended to be the same enzyme, consistent claim language is required for clarity.

9. Previous objection to the specification for the description of ORF28 being inconsistent between Table II and Figure 3B is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant notes that the figure appears to have a typographical error; yet no effort has been made to correct such an error in the drawings. Consistency is required. As previously noted, in Table II, ORF 28 is disclosed as being 335 amino acids long; however, in Figure 3B, ORF 28 is described as being 350 amino acids long. The cause for this discrepancy is unclear.

10. Previous objection to the amendment filed on December 5, 2001, which amended Table II, is maintained. Applicant did not address this issue previously. Table II contains a deletion in

Art Unit: 1652

the last line of the original text that is “[102]”; however this text is not replaced and Table II appears to be incomplete. Appropriate correction or explanation is required.

Withdrawn - Claim Objections

11. Previous objection to Claims 24-50 for containing non-elected subject matter is withdrawn by virtue of Applicant’s amendment.
12. Previous objection to Claim 25 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant’s cancellation of said claim.
13. Previous objection to Claims 26-27 for using improper verb tenses is withdrawn by virtue of Applicant’s amendment to said claims.
14. Previous objection to Claim 30 for improper English is withdrawn by virtue of Applicant’s amendment to said claim.
15. Previous objection to Claim 32 for improper English is withdrawn by virtue of Applicant’s amendment to said claim.
16. Previous objection to Claim 36 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant’s cancellation of said claim.

Art Unit: 1652

17. Previous objection to Claim 39 as a duplicate claim of Claim 30 is withdrawn by virtue of Applicant's cancellation of said claim.

18. Previous objection to Claim 40 for improper English is withdrawn by virtue of Applicant's amendment to said claim.

19. Previous objection to Claim 41 for a typographical error is withdrawn by virtue of Applicant's cancellation of said claim.

20. Previous objection to Claims 41-42 for a typographical error is withdrawn by Applicant's amendment and/or cancellation of said claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

21. Previous rejection of Claims 24-50 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to the phrase "a C-1027 biosynthesis gene cluster open reading frame" is withdrawn. By virtue of Applicant's amendment, the phrase "a C-1027 biosynthesis gene cluster open reading frame 28 (ORF 28)" means *any* O-methyltransferase and the phrase "a *Streptomyces* C-1027 biosynthesis gene cluster open reading frame 28 (ORF 28)" means *any* naturally occurring O-methyltransferase from a *Streptomyces* species.

22. Previous rejection of Claims 41-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "hydrase" is withdrawn by virtue of Applicant's amendment removing this term from the claims.

Art Unit: 1652

23. Previous rejection of Claims 41-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the requirement for “proline oxidase” is withdrawn by virtue of Applicant’s amendment removing this requirement from the claim limitations.

24. Previous rejection of Claims 41-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for references to “an époxyde hydase”, “a monooxygenase”, “an iron-sulfur flavoprotein”, “a p-450 hydroxylase”, “an oxidoreductase, and “a proline oxidase” is withdrawn by virtue of Applicant’s amendment removing this requirement from the claim limitations.

25. Previous rejection of Claim 45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the purpose of the limitation of ORF 3 is withdrawn by virtue of Applicant’s amendment to Claim 44, from which Claim 45 depends.

26. Previous rejection of Claims 46-50 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant’s cancellation of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112

27. Previous rejection of Claim 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "substantially" is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the term is per se definite based on legal precedent. The Examiner disagrees. No term is per se definite or indefinite. In the instant case, the term is indefinite because, as previously noted, it is unclear which polypeptides are include – all those in Tables I, II, and III? Just Tables I and II? No description in the specification gives even an indication of how many polypeptides of the

Art Unit: 1652

gene cluster are required to be a substantial portion of the polypeptides. Without any way to discern what is meant by the term “substantially”, the term is indefinite as used in the instant claims. Clarification is required as previously noted.

28. Previous rejection of Claim 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “enediynes analogue” is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the term must be read in light of the specification, that the term is art-recognized, and that numerous other patents use the term “analogue” in their claims. All these are true, however, in the instant case, the specification gives not indication of what analogues are included. As previously noted, “How similar must a compound be to an enediyne compound to be considered and analogue? Is the chromophore sufficient? Is the protein sufficient? How similar to either of these structures must the claimed analogue be?” While the term “analogue” is recognized in the art, the art does not clearly set forth the metes and bounds indicated by the term in each instant. This is precisely why the specification is necessary to define terms. And while the term “analogue” is used in other patent claims clearly, it is not the case here. Firstly, the term is “an enediyne analogue” which is distinct from “a nucleoside analogue” or “a capsaicin analogue”. Secondly, those patent claims are read in light of those specifications and are considered clear. As previously noted, this is not the case here as the instant specification gives no indication of structural analogues? How much structure must be maintained? Functional analogues? What function must be maintained? Thus, for all of the above reasons, the instant rejection is maintained.

Art Unit: 1652

29. Claims 42-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims all depend either directly or indirectly on Claim 41, which is cancelled. Thus, Claims 42-45 are unclear as to the scope they encompass. Clarification is required.

30. Previous rejection of Claims 24, 26-35, 37, 38, 40, and 42-45 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicant's arguments have been fully considered and are not deemed persuasive for the following reasons. Applicant argues that

“Claims 24-50, as amended herein, are directed to methods that utilize a ‘an O-methyltransferase encoded by a Streptomyces C-1027 biosynthesis gene cluster open reading frame 28’. One skilled in the art, reading the original disclosure would reasonably discern the limitation ‘a Streptomyces [sic] C-1027 biosynthesis gene cluster open reading frame 28’ in the original disclosure” (emphasis in original).

This is not found persuasive because the disclosure of a single representative species of the claimed genus of any *Streptomyces* C-1027 ORF28 (O-methyltransferase) does not adequately describe the claimed genus. As previously noted,

“In the instant specification, one species of the claimed genus of methods is fully described. However, this species does not predictably identify either the structure of specific function of other members of the genus. Particularly, polypeptides from other enediyne-synthesizing organisms, wherein said polypeptides are analogous to ORF 28, cannot be predicted from the disclosed ORF 28 in either their structure or function. While the structure may be similar, it will not be identical and variations cannot be predicted. While the function may be similar, it will not be identical using a different substrate to produce a different product. Thus, the ability of the ORF 28 disclosed to predict other ORF 28 polypeptide is low. Therefore, the single disclosed species of the genus of methods claimed does not adequately describe the genus.”

Art Unit: 1652

The instant claims are not limited to using the disclosed ORF28 (as translated from SEQ ID NO:2, nucleotides 4188-5189) but *any* O-methyltransferase encoded by any *Streptomyces* C-1027 gene cluster. No generic description of either O-methyltransferases from C-1027 gene clusters or *Streptomyces* sequences is found in the instant specification. Thus, one of skill in the art would be unable to predict the structure of the other members of the claimed genus.

Applicant further argues:

“Similarly, with respect to the substrate limitation, one suitable substrate for O-methyltransferase is illustrated in Figure 3B. One of ordinary skill in the art would recognize a number of other analogues of the illustrated substrate that would also be suitable for modification by O-methyltransferase. Moreover, one skilled in the art, reading the original disclosure would reasonably discern the use of O-methyltransferase [sic] with other substrates.”

This argument concerning the substrate required for the claims is also not found persuasive. One O-methyltransferase is indicated for ORF28 (the Examiner notes here that the description of ORF28 in Figure 3B is a typographical error as admitted by Applicant and indicates ORF28 as translated from SEQ ID NO:2, nucleotides 4188-5189). The genus of substrates required for the instant claims is a set of molecules, presumed to be analogues by Applicant while no such limitation is found in the claims, that act as substrates for *any* O-methyltransferase of *any* C-1027 ORF28. This genus has not been described structurally whatsoever. Moreover, the claims use only a functional description, which amounts to no more than a try-it-and-see. These limitations do not limit the claimed genus of substrates to that which are adequately described by the specification as originally filed.

For these reasons, the instant claims lack adequate written description for the genus of O-methyltransferases, limited to *Streptomyces* C-1027 O-methyltransferases, and for the genus of substrates for any O-methyltransferase for any C-1027 ORF28.

Art Unit: 1652

31. Previous rejection of Claims 24, 26-27, 30, 37, 40, and 42-45 under 35 U.S.C. § 112, first paragraph, scope of enablement, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that using two or more enzymes in an *ex vivo* system is routine. Applicant argues that "considerable guidance" is presented for the reconstitution of the C-1027 biosynthetic machinery by virtue of Figures 1-4; the Examiner disagrees as none of these figures describe which enzymes to be included, how to reconstitute said enzymes so they function in a "physiological buffer system", as Applicant describes as routine, and which cofactors might be necessary. Applicant states "Working examples (WANDS Factor 3) are provided"; this statement is simply false since nowhere is a substrate combined with ORF28 *ex vivo* in the specification. Applicant argues that "the nature of the invention is relatively straightforward (Wands Factor 4) being directed to the use of C-1027 enzyme(s) to chemically modify target substrates"; the Examiner disagrees. As previously noted by the Examiner:

"The nature of the invention is a complex system of assembly-line-type enzymes that function together to produce a final complex compound; moreover, the exact functions and sequence of reactions is not wholly understood."

Consider all the enzymes of Figures 1-3, consider all the genes involved in Figure 5A.

Straightforward is not considered an appropriate characterization of the system by the Examiner whatsoever. While the Examiner agrees that PKS and NRPS systems are well-developed as a field of art, with each newly identified gene cluster, new "rules" are found. And moreover, the instant gene cluster does not fit a particular "pattern" of PKS or NRPS, thus, these templates cannot be expected to offer all understanding simply by the state of the art. Applicant further argues that the predictability in the field is good based on the ability to swap modules in PKS

Art Unit: 1652

systems. No modules have been identified in the instant gene cluster, thus, this predictability does not translate to the instant system.

For all of the above reasons, the instant rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 101

32. Previous rejection of Claims 24, 26-27, 30, 40, and 42-45 under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the requirement in Claim 24 that the O-methyltransferase be expressed by a vector introduces the hand or man into the claimed invention. The Examiner disagrees. This claim limitation merely described the O-methyltransferase used. Recombinant O-methyltransferases can be identical to naturally occurring O-methyltransferases. As such, this "recombinant" limitation adds no hand-of-man limitation.

Maintained - Claim Rejections - 35 U.S.C. § 103

33. Previous rejection of Claims 24-27, 38, 40, and 42-45 under 35 U.S.C. § 103(a) as being unpatentable over Hu *et al.* (IDS #14 reference 10) is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the art does not teach expressing ORF28 in a vector so Hu *et al.* does not teach all the limitations of the claims. This is not found because this vector limitation merely describes the ORF28 used, which is not distinct from a naturally occurring one, and is not a real method step. Thus, as previously noted, Hu *et al.* teach the claimed method with all its limitations.

Withdrawn - Double Patenting

34. Previous note of Claim 39 being a substantial duplicate of Claim 30 is herein moot by virtue of Applicant's cancellation of Claim 39.

Conclusion

35. Claims 24, 26-35, 37, 38, 40, and 42-45 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M. Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

Art Unit: 1652

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

March 7, 2005